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(54) Title: SULFINYL AND SULFONYL SUBSTITUTED 3-BENZAZEPINES (57) Abstract Sulfinyl and sulfonyl substituted 3-benzazepine compounds are useful in treating and preventing emesis. Particular compounds of this invention are 7-methyl-sulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine and 8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine.		

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SULFINYL AND SULFONYL SUBSTITUTED 3-BENZAZEPINES

This invention relates to sulfinyl and sulfonyl substituted benzazepine compounds for use in treating emesis.

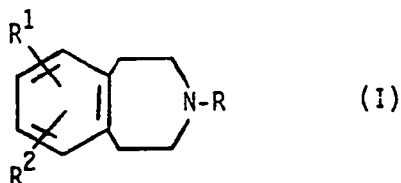
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These compounds are known in the art and may be prepared as shown in European Patent Application 86309846.3. They have been reported as having utility in the treatment of gastrointestinal diseases. It has now been found that the sulfinyl and sulfonyl substituted benzazepine compounds are useful therapeutically for treating or preventing emesis.

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According to the present invention there is provided the use of a compound of the formula (I):

25



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in which:

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R is hydrogen, C₁-C₆alkyl or C₃-C₅alkenyl;

R¹ is SO₂R³, SO₂R³ or SO₂NR⁴R⁵;

R² is hydrogen, halogen, CF₃, C₁-C₆alkyl or R⁶O-;

R³ is C₁-C₆alkyl or CF₃;

R⁴ and R⁵ are hydrogen or C₁-C₆alkyl; and

1 R⁶ is hydrogen, C₁-C₆alkyl or C₁-C₆alkanoyl,
provided that when R¹ is SO₂NH₂, R² is R⁶O-, halogen,
CF₃ or C₁-C₆alkyl,
5 or a pharmaceutically acceptable acid addition salt
thereof in the manufacture of a medicament for treating or
preventing emesis.

Particular compounds of formula (I) are those
in which R¹ is in the 7-position. Further particular
10 compounds of formula (I) are those in which R¹ is in the
7-position and R² is in the 8-position.

A group of compounds of formula (I) is that in
which R¹ is SO₂R³ or SO₂NR⁴R⁵, R² is hydrogen, alkoxy or
hydroxy, R³ is methyl and R is hydrogen and, in addition,
15 R¹ may be in the 7-position and R² may be in the
8-position.

Specific compounds of this invention are:

8-hydroxy-7-methylsulfonyl-2,3,4,5-tetrahydro-
1H-3-benzazepine;
20 7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-
benzazepine;
8-hydroxy-7-(N-methylsulfamoyl)-2,3,4,5-tetra-
hydro-1H-3-benzazepine;
25 8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-
3-benzazepine;
6-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

The compounds of formula (I) form pharmaceuti-
cally acceptable acid addition salts with organic or
30 inorganic acids. Examples of these acids are
hydrochloric, hydrobromic, sulfuric, phosphoric, acetic,
tartaric, citric, maleic, lactic, oxalic, succinic,
methanesulfonic, and benzenesulfonic acids. The salts are
formed according to methods known to the art. If the
35 product is isolated as an acid addition salt, it may be
treated with an inorganic or organic base, such as aqueous
sodium hydroxide, sodium carbonate, triethylamine, etc.,

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1 and converted to the corresponding free base. The base
can then be treated with an appropriate acid, for example
in an aqueous miscible solvent, such as a lower alkanol
preferably methanol or ethanol, to give the desired salt.

5 The effect of the pharmacologically active
compounds of this invention on emesis is demonstrated in
the following test procedure.

Method for Determination of the Anti-emetic Effect in the
Conscious Dog

10 Compounds are administered orally or parenterally
to proven apomorphine-sensitive dogs of either sex. After
the appropriate time has elapsed (determined by a peak
time study), apomorphine hydrochloride (0.1 mg/kg, s.c.)
is administered and the frequency of emesis is observed
15 and recorded for the next forty minutes. Emesis is
defined as the actual expulsion of stomach contents.

The control group of dogs, also apomorphine-
sensitive, receive the test vehicle and apomorphine
hydrochloride (0.1 mg/kg, s.c.) Emesis is recorded as
20 with the test animals.

The mean frequency of emesis for the control and
test groups is calculated. A value for each test group is
then obtained which expresses the percentage increase or
decrease in frequency of emesis relative to controls. An
25 effective dose-50% is calculated. The ED₅₀ refers to
the dose that decreases emesis induced by apomorphine by
50%.

The pharmacologically active compounds of
formula (I) can be administered orally or parenterally.
30 Preferably, these compounds are administered in conven-
tional dosage unit forms prepared by combining an appro-
priate dose of the compound with standard pharmaceutical
carriers. The dosage units will contain the active
ingredient in an effective amount selected from about 1 mg.
35 to about 250 mg., preferably 10 mg. to 100 mg.

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The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent can include any time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

10

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a trousse or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 g. If a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampul or an aqueous or nonaqueous liquid suspension.

20

The pharmaceutical compositions are prepared by conventional techniques involving procedures such as mixing, granulating and compressing when necessary or variously mixing and dissolving the ingredients as appropriate to the desired composition.

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The method of treating and preventing emesis in accordance with this invention comprises administering internally to a subject in need of said treatment an effective amount of a compound of formula (I), in particular, 7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 6-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine, 7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine, or 8-methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine or a pharmaceutically acceptable acid addition salt thereof.

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1 The compound will preferably be administered in a
dosage unit form orally or parenterally. Advantageously
equal doses will be administered one to four times daily
with the daily dosage regimen being from about 1 mg. to
5 about 1000 mg., preferably from 10 mg. to 400 mg.

One skilled in the art will recognize that in
determining the amounts of the compound needed to produce
the desired pharmacological effect without toxic side
effects, the activity of the particular compound as well
10 as the size of the host animal must be considered.

The following examples illustrate the invention
but are not to be construed as limiting the scope
thereof. Temperatures are in degrees Centigrade unless
15 otherwise stated.

EXAMPLE 1

8-Hydroxy-7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

A mixture of 3-methoxyphenylacetic acid (47.7 g,
0.287 m), thionyl chloride (50 ml) and N,N-dimethylforma-
20 mide (6 drops) in toluene (500 ml) was stirred for 16
hours at 25° and concentrated in vacuo to afford 3-methoxy-
phenylacetyl chloride. The acetyl chloride was dissolved
in chloroform (100 ml) and added to a solution of amino-
acetaldehyde dimethyl acetal (32.1 g, 0.306 m) and tri-
25 ethylamine (32.4 g, 0.320 m) in chloroform (500 ml) stirred
at 5°. The mixture was stirred at 25° for 16 hours, washed
with water, 1.5N hydrochloric acid and water, dried with
magnesium sulfate and concentrated in vacuo to give
N-(2,2-dimethoxyethyl)-3-methoxybenzeneacetamide.

30 A solution of the benzeneacetamide (70 g,
0.277 m) in acetic acid (180 ml) was added with stirring
to concentrated hydrochloric acid (120 ml). The mixture
was stirred for 16 hours, diluted with ice/water and
filtered. The filter cake was dissolved in methylene
chloride which was washed with water, dried with magnesium
35 sulfate and concentrated in vacuo to give 2,3-dihydro-8-
methoxy-2-oxo-1H-3-benzazepine.

1 A mixture of 2,3-dihydro-8-methoxy-2-oxo-1H-
3-benzazepine (12 g, 0.063 m) and 10% palladium-on-carbon
5 (1.2 g) in acetic acid (200 ml) was shaken in an atmos-
phere of hydrogen (60 psi), degassed, filtered and
concentrated in vacuo. The residue was dissolved in
methylene chloride, washed with water, dried with magnesium
sulfate and concentrated in vacuo. The residue was
trituated with ether and filtered to give 8-methoxy-
2-oxo-2,3,4,5-tetrahydro-1H-3-benzazepine.

10 A suspension of 8-methoxy-2-oxo-2,3,4,5-tetra-
hydro-1H-3-benzazepine (20.4 g, 0.105 m) in tetrahydrofuran
(500 ml) was added to 1M borane in tetrahydrofuran (300
ml) stirred at 5°. The mixture was heated to reflux for 2
15 hours, cooled, treated with 3N hydrochloric acid (300 ml),
concentrated in vacuo to remove tetrahydrofuran and heated
to reflux for 1 hour. The mixture was concentrated in
vacuo, filtered and the filter cake was dissolved in
methanol, heated to reflux, dried with magnesium sulfate
20 and concentrated in vacuo to afford 7-methoxy-2,3,4,5-
tetrahydro-1H-3-benzazepine hydrochloride, m.p. 229-231°.

A mixture of 7-methoxy-2,3,4,5-tetrahydro-
1H-3-benzazepine hydrochloride (4.3 g, 0.02 m) and sodium
acetate (3.3 g, 0.04 m) in acetic anhydride (13 ml) was
25 refluxed and stirred for 16 hours, concentrated in vacuo
and partitioned between methylene chloride and water. The
organic phase was dried with magnesium sulfate, filtered
and concentrated in vacuo to give 3-acetyl-7-methoxy-
2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 89-90°.

30 3-Acetyl-7-methoxy-2,3,4,5-tetrahydro-1H-
3-benzazepine (2.3 g, 0.01 m) was added to chlorosulfonic
acid (6 ml) which was stirred at 0°; the mixture was
allowed to warm to 25° and stirred for 16 hours. The
reaction was carefully poured into ice water and extracted
35 with methylene chloride. The methylene chloride extracts
were combined, washed, dried with magnesium sulfate and
concentrated in vacuo to give 3-acetyl-7-chlorosulfonyl-8-
methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 153-160°.

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1 3-Acetyl-7-chlorosulfonyl-8-methoxy-2,3,4,5-
tetrahydro-1H-3-benzazepine (3 g, 0.007 m) was treated
with concentrated ammonium hydroxide (10 ml), stirred for
2 hours and filtered to give 3-acetyl-8-methoxy-7-sulfa-
5 moyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 260-263°.

The sulfonamide (2.3 g, 0.007 m) was suspended in
3N hydrochloric acid and heated to reflux for 16 hours.
The mixture was concentrated in vacuo and the residue
crystallized from methanol to give 8-methoxy-7-sulfamoyl-
10 2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, m.p.
270-274°.

8-Methoxy-7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-
benzazepine hydrochloride (1.5 g, 0.005 m) was dissolved
in 48% hydrobromic acid (15 ml), refluxed for 2 hours and
15 concentrated in vacuo. The residue was triturated with
acetone and then recrystallized from methanol to give
8-hydroxy-7-sulfamoyl-2,3,4,5-tetrahydro-1H-3-benzazepine
hydrobromide, m.p. 315-320° (decomp.).

EXAMPLE 2

20 8-Hydroxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-
benzazepine.

Method A

3-Acetyl-7-chlorosulfonyl-8-methoxy-2,3,4,5-tetra-
hydro-1H-3-benzazepine (18 g, 0.056 m) was added in
25 portions to a mixture of sodium sulfite (8.8 g, 0.069 m)
and sodium bicarbonate (10.8 g, 0.115 m) in water (36 ml)
stirred at 70°C. There was a vigorous evolution of gas
after each addition. The mixture was stirred for fifteen
minutes, treated with iodomethane (8.5 ml, 0.136 m) and
30 refluxed for forty-five minutes. The mixture was parti-
tioned between methylene chloride and water. The methylene
chloride phase was washed with water, dried with sodium
sulfate and concentrated in vacuo to give 3-acetyl-8-
methoxy-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzaze-
35 pine, m.p. 159-162°C.

1 Method B

3-Acetyl-7-chlorosulfonyl-8-methoxy-2,3,4,5-
tetrahydro-1H-3-benzazepine (4 g, 0.013 m) was dissolved
in glacial acetic acid (80 ml), treated with stannous
chloride dihydrate (11.6 g, 0.05 m) and concentrated
hydrochloric acid (16 ml) and stirred at 75° for 1 hour.
The mixture was cooled, poured into ice water and extract-
ed with ethyl acetate. The combined ethyl acetate extract
was washed, dried with magnesium sulfate and concentrated
in vacuo to give a mixture of 3-acetyl-7-mercapto-8-
methoxy-2,3,4,5-tetrahydro-1H-3-benzazepine and the
corresponding disulfide.

The crude mixture (3 g) was dissolved in ethanol
and treated with sodium borohydride (2 g, 0.05 m) to
effect reduction of the disulfide to the mercaptan.

Methyl iodide (2 g, 0.014 m) was added and the reaction
mixture was stirred at 25° for 1 hour. The mixture was
concentrated, partitioned between water and methylene
chloride and the combined methylene chloride extract was
washed, dried with magnesium sulfate and concentrated in
vacuo to give 3-acetyl-8-methoxy-7-methylthio-2,3,4,5-
tetrahydro-1H-3-benzazepine, m.p. 138-140°.

3-Acetyl-8-methoxy-7-methylthio-2,3,4,5-tetra-
hydro-1H-3-benzazepine (1.1 g, 0.004 m) dissolved in
methylene chloride (10 ml) was treated with 3-chloro-
perbenzoic acid (1.4 g, 0.008 m) and stirred for 1 hour.
The mixture was extracted with 5% aqueous sodium carbonate,
washed with water, dried with magnesium sulfate and
concentrated in vacuo to give 3-acetyl-8-methoxy-7-methyl-
sulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine, m.p. 162-164°.

3-Acetyl-8-methoxy-7-methylsulfonyl-2,3,4,5-
tetrahydro-1H-3-benzazepine (1 g, 0.003 m), prepared as in
Method A or B, in 48% hydrobromic acid (15 ml) was heated
to reflux for 16 hours and concentrated in vacuo. The
residue was triturated with acetone and recrystallized
from methanol-water to give 8-hydroxy-7-methylsulfonyl-

1 2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide, m.p.
300° (decomp.).

Alternatively, 3-acetyl-8-methoxy-7-methyl-
sulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine was treated
5 with 3N hydrochloric acid to give 8-methoxy-7-methyl-
sulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride,
m.p. 228.5-229.5°. Refluxing this compound with 48%
hydrobromic acid gave 8-hydroxy-7-methylsulfonyl-2,3,4,5-
10 tetrahydro-1H-3-benzazepine hydrobromide.

EXAMPLE 3

7-Methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

Following the procedure of Examples 1 and 2,
2,3,4,5-tetrahydro-1H-3-benzazepine was converted to
3-acetyl-7-chlorosulfonyl-2,3,4,5-tetrahydro-1H-3-benza-
15 zepine and then to 3-acetyl-7-methylsulfonyl-2,3,4,5-tetra-
hydro-1H-3-benzazepine which was hydrolyzed with hydro-
chloric acid to give 7-methylsulfonyl-2,3,4,5-tetrahydro-
1H-3-benzazepine hydrochloride, m.p. 275-277°C.

EXAMPLE 4

20. 7-Methylsulfonyl-2,3,4,5-tetrahydro-1H-3-
benzazepine methanesulfonate (10 mg) is mixed with 75 mg
of lactose and 2 mg of magnesium stearate. The resulting
mixture is filled into a hard gelatin capsule.

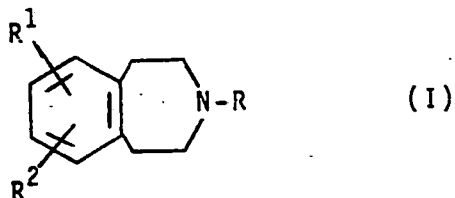
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1 CLAIMS:

1. The use of a compound of the formula:



in which:

R is hydrogen, C₁-C₆alkyl or C₃-C₅alkenyl;
 R¹ is SO₂R³, SO₂R³ or SO₂NR⁴R⁵;
 R² is hydrogen, halogen, CF₃, C₁-C₆alkyl or R⁶O-;
 R³ is C₁-C₆alkyl or trifluoromethyl;
 R⁴ and R⁵ are hydrogen or C₁-C₆alkyl; and
 R⁶ is hydrogen, C₁-C₆alkyl or C₁-C₆alkanoyl,
 provided that when R¹ is SO₂NH₂, R² is R⁶O-,
 halogen, CF₃ or C₁-C₆alkyl,

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or a pharmaceutically acceptable acid addition salt thereof, in the manufacture of a medicament for treating or preventing emesis.

25 2. The use of a compound as defined in claim 1 in which R¹ is in the 7-position.

30 3. The use of a compound as defined in claim 1 in which R² is in the 8-position and R¹ is in the 7-position.

35 4. The use of a compound as defined in claim 1 in which R¹ is SO₂R³ or SO₂NR⁴R⁵, R² is hydrogen or C₁-C₆alkoxy, R³ is methyl, R is hydrogen, R² is in the 8-position and R¹ is in the 7-position.

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1 5. The use of a compound as defined in claim 1
said compound being 7-methylsulfonyl-2,3,4,5-tetrahydro-
1H-3-benzazepine.

5 6. The use of a compound as defined in claim 1
said compound being 8-methoxy-7-methylsulfonyl-2,3,4,5-
tetrahydro-1H-3-benzazepine.

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INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/01169

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(4): A61K 31/55 U.S.Cl.: 514/213						
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border-right: 1px solid black; padding: 5px;">U.S.</td> <td style="padding: 5px;">514/213</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black; margin: 5px 0;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	U.S.	514/213
Classification System	Classification Symbols					
U.S.	514/213					
CAS ON LINE						
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹						
Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³				
A	U.S., A, 3,689,649 (DIETRICH) published 05 September 1972. See entire document.	1-13				
A	U.S., A, 4,024,128 (KOCH) published 17 May 1977. See entire document.	1-13				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>						
IV. CERTIFICATION						
Date of the Actual Completion of the International Search 28 JULY 1988		Date of Mailing of this International Search Report 25 JUL 1988				
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